DEVELOPMENT OF ORALLY ADMINISTERED TRAZODONE HYDROCHLORIDE LOADED SOLID LIPID NANOPARTICLE AND NANO STRUCTURED LIPID PARTICLES FOR THE TREATMENT OF DEPRESSION

SYNOPSIS OF THE THESIS

Submitted by

Neha Sharma

Registration No.: AU20PYPhD0040

Under supervision of

Dr. ABHISHEK SONI

In Partial Fulfillment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

SCHOOL OF PHARMACY

ABHILASHI UNIVERSITY

CHAIL-CHOWK, MANDI (H.P.) – 175028

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DECLARATION

I hereby declare that the dissertation synopsis entitled **"Development Of Orally Administered Trazodone Hydrochloride Loaded Solid Lipid Nanoparticle And Nano Structured Lipid Particles For The Treatment Of Depression"** to be submitted for the partial fulfillment of the Degree of Doctor of Philosophy is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associateship or fellowship of similar other titles. It has not been submitted to any other University or Institution for the award of any degree or diploma.

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Place: Chail. Chowk

Date: 04/02/2022

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INTRODUCTION

1.0 Introduction

1.1 Purpose of the study

The purpose of the present study shall be to investigate and compare the potential of trazodone HCl-loaded solid lipid nanoparticle and nanostructure lipid particles for the treatment of depression via the non-invasive oral route of administration. SLNs and NLC are known to enhance the oral bioavailability of a variety of drugs and also have been established to deliver a wide range of drugs to the brain, i.e., the site of action for neuroprotective agents. The present study also aims to explore and compare the brain targeting potential of trazodone hydrochloride loaded solid lipid nanoparticle and Nanostructured lipid particles besides enhancing their bioavailability, Reduced first-pass metabolism, bypassing the P-glycoprotein efflux pumps, improving the half-life, reducing its dosage, restricting the off-target distribution, preventing undesired plasma peak, the shorter onset of action and larger duration of action, modulated and controlled drug release, and improving the benefit to risk ratio. In this study, we shall explore and compare the antidepressant effect of trazodone hydrochloride-loaded solid lipid nanoparticles and Nanostructured lipid particles in mice models following oral administration.

1.2 Background

Depression is a disorder of major public health importance, in terms of its prevalence and the suffering, dysfunction, morbidity, and economic burden. Depression is more common in women than men. The report on Global Burden of Disease estimates the point prevalence of unipolar depressive episodes to be 1.9% for men and 3.2% for women, and the one-year prevalence has been estimated to be 5.8% for men and 9.5% for women. It is estimated that by the year 2020 if current trends for demographic and epidemiological transition continue, the burden of depression will increase to 5.7% of the total burden of disease and it would be the second leading cause of disability-adjusted life years (DALYs), second only to ischemic heart disease.[1] Given the morbidity, depression as a disorder has always been a focus of attention of researchers in India. Various authors have tried to study its prevalence, nosological issues, psychosocial risk factors including life events, symptomatology in the cultural context, comorbidity, psychoneurobiology, treatment, outcome, prevention, disability, and burden.

Some of the studies have also tried to address various issues in children and the elderly. Many studies have estimated the prevalence of depression in community samples and the prevalence rates have varied from 1.7 to 74 per thousand population.

Depression is a common mental disorder that is characterized by a persistent feeling of sadness, low self-esteem, disturbed appetite, suicidal thoughts, insomnia, and loss of interest [1]. Depression is caused by several aspects which include pathological effects, social activities such as drug and alcohol abuse, and biological factors [2]. According to research done by the World Health Organization (W.H.O) in 2017, more than 300 million people (approximately 4.4% of the world's population) suffer from depression [1] making it one of the top two causes of disability-adjusted life years currently [2]. Pathological causes of depression include a chemical imbalance in the brain, energy metabolic decline, and alteration in body hormones [3]. According to the serotonin hypothesis, depression is a result of dysfunctional serotonergic activities [4] which results in reduced serotonin levels in the brain. Several classes of antidepressant therapy that are currently on the market include selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors. SSRIs such as paroxetine, vilazodone, and fluvoxamine are first-line treatment options in adults with depression, albeit with several contraindications [5]. The side effects of the current medication include delayed therapeutic onset, low bioavailability, erectile dysfunction, weight gain, dry mouth, nervousness, and insomnia. Some currently approved antidepressant drugs pass through extensive first-pass metabolism which results in reduced oral bioavailability [5]. The time taken by the drug to reach the saturation point is usually prolonged, resulting in delayed therapeutic onset and reduced therapeutic efficacy. Furthermore, as the bioavailability is low, higher doses are required, leading to an increased prevalence of side effects. The therapeutic effect is also limited because of the presence of the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB). Traditional medicines have a limited capacity of crossing the BBB and BCSFB [6]. According to current research, nanotechnology-based delivery platforms can be employed to ameliorate the above-mentioned limitations [7,8]. The uses of nanomedicine, biopolymers, and nanocarriers have gained significant attention to overcoming these gaps [7].

Nano-based drug delivery strategies offer various advantages in the treatment of chronic diseases by site-specific and targeted delivery, thereby improving the efficacy of approved formulations [7]. Additionally, nanoparticles can improve plasma bioavailability profiles, further enhancing a sustained delivery of antidepressants, resulting in reduced side effects on account of lowered dosing frequencies. Nanomedicine has been used to overcome the limitations of the BBB, as they penetrate through it due to their small size ≤100 nm [9]. Furthermore, nanoparticles can target specific receptors enabled by complexation to ligands such as transferrin and glutathione for improving therapeutic efficacy [9,10,11]. In this review, we discuss different drug carriers, ligands, and biopolymers that can improve the bioavailability and therapeutic efficacy of antidepressants by reducing undesirable side effects and dosing frequencies, to achieve safe, desired clinical outcomes.

1.2.1. Designing Sustained-Release Formulations for the Delivery of Antidepressant Drugs

Biopolymer-based nano-drug delivery systems have been shown to lower antidepressant drug toxicity and dosing frequency, as they can be designed to exhibit controlled drug release [12]. According to the literature, drug solubility, specificity, improved bioavailability, bio-distribution, and controlled release of antidepressant drugs have been achieved through the use of biopolymer-based drug delivery [12]. Nanocarriers influence the bioavailability and therapeutic efficacy of antidepressants depending on the route of administration used. They can enhance the drug stability, encapsulating rate, drug solubility, and circulation time of antidepressants in the body [13].

1.2.2 The Oral Route of Antidepressant Drug Delivery

The oral route of administration is the route of choice for the delivery of chronic therapy due to good patient compliance, low cost, and ease of administration. However, enzymatic barriers in the gastrointestinal tract harm the effectiveness of oral drug delivery. The oral route of delivery limits drug half-life due to the hepatic first-pass effect and other factors, resulting in reduced drug efficacy [14,15]. The BBB is a complex physiological barrier, which hinders the penetration of substances into the brain. To improve neuro-availability, biopolymers can be

employed to improve drug permeability through the BBB. Biopolymers such as polysaccharides present attractive strategies for the oral delivery of antidepressants due to their desired characteristics which include; sustained drug release profiles, small size, stability, biodegradability, biocompatibility, and limited toxicity [16].

A study was conducted in which venlafaxine was delivered in a copolymeric platform composed of sodium alginate and hydroxypropyl methylcellulose. The main focus of the study was to improve the oral bioavailability of venlafaxine as it is freely soluble in water, undergoes first-pass metabolism, has a narrow absorption window, and exhibits a short half-life [14]. The results showed a sustained release profile as well as improved oral bioavailability and mucoadhesive properties of the antidepressant, resulting in improved drug efficacy [14]. The drug diffusion release in the above-mentioned study was dependent on the swelling behaviour of the biopolymer and the concentration of sodium alginate employed. A high concentration of sodium alginate resulted in controlled release hence improved half-life [14]. Another study showed that sodium alginate delays gastric emptying, hence increased drug circulation time when imipramine was encapsulated into sodium alginate-based nanoparticles for oral delivery [17]. Moreover, using chitosan to improve the oral bioavailability of escitalopram demonstrated reduced first-pass metabolism [18]. The results showed reduced hepatic first-pass metabolism, with shielding from enzymatic degradation. The in vitro study which was done using a dialysis membrane exhibited improved drug circulating time in the body, hence sustained release over 24 h. The oral bioavailability of the antidepressant was improved due to the mucoadhesive properties of the biopolymer. The drug release was 98.4 ± 1.07%, the particle size ranged from 60–115 nm and the neuro- availability of the antidepressant was improved. The size and biodegradability properties of chitosan affect its bioactivity on the BBB. Hence, drug-loaded chitosan nanoparticles can penetrate through the BBB for drug delivery against neurological disorders.

Chitosan nanoparticles are also biocompatible, biodegradable, mucoadhesive, and non-toxic, which makes them suitable for designing drug delivery vehicles for the treatment of neurological conditions [18,19]. Erum et al., 2016, formulated and evaluated fluoxetine HCL microspheres using chitosan and arabinoxylan as the biopolymers. These biopolymers are known to be non-toxic, biocompatible, biodegradable, and have improved entrapment

efficiency. The cationic property of chitosan allows it to react with polyanions giving rise to polyelectrolyte complexes with arabinoxylan biopolymers. The percentage yield was improved to 93% and the drug entrapment rate was improved to about 77%. In vitro studies proved that chitosan improved the drug release of the antidepressant due to the swelling properties of the biopolymers. Hence, a copolymer of chitosan and arabinoxylan can be employed during the formulation of fluoxetine HCL oral microspheres in a 2:1 ratio, respectively, to obtain a sustained release profile. Moreover, chitosan has a high drug entrapping efficiency and the percentage yield is directly proportional to the concentration of the biopolymers [20-21]. This might result in improved neuro-bioavailability of the antidepressants.

Moreover, PEGylated oral nanoparticles exhibit enhanced half-life, oral bioavailability, and water solubility of bioactive molecules, reduced hepatic first-pass metabolism, and premature leaking of the bioactive agent. PEGylation also increases the molecular weight of the drug, hence slowing down its clearance rate in the kidney [22,23]. PEGylated polymeric nanoparticles penetrate the brain better, as compared to nanoparticles coated with polysorbate 80 [24]. This is because PEG is covalently attached to the polymer, preventing the pre-leakage of the bioactive agent from the PEGylated polymeric nanoparticles whilst polysorbate 80 is prone to adsorption [24].

Abourehab et al. conducted a study where they synthesized self-assembled biodegradable polymeric micelles to improve dapoxetine-loaded PEG-PLGA delivery of the antidepressant nano micelles across the BBB. The study showed that PEGylation might protect the drug-loaded nanoparticle from uptake by the reticuloendothelial system, hence improving the oral bioavailability and the circulation half-life of the drug. The extended circulation half-life allows more absorption of loaded PEG-PLGA via the bloodstream. The study further demonstrated that PEGylation of the nanoparticles improves the rate of accumulation of the antidepressant in the brain and its absorption rate on account of reduced first-pass metabolism. Furthermore, the improved half-life ameliorates the accumulation of the antidepressant, hence increasing its cerebral concentration [25-30].

1.2.4 Nanocarriers Employed as Therapeutic Delivery Platforms of Antidepressants

Nanocarriers possess attractive properties which include a high surface-area-to-volume ratio, controlled drug release, targeted delivery, multi-functionality, and a great potential for surface modification [31-35]. Moreover, their nano size has conferred on them the ability to penetrate the BBB and target the brain, rendering them desirable for Neurotherapy and diagnosis. Nanocarriers can be employed to enhance drug solubility, circulating time, stability, and the biocompatibility of antidepressants targeted to the brain [32, 35]. Moreover, nanocarriers minimize hepatic first-pass metabolism and protect bioactive agents from hydrolytic and enzymatic degradation. They show great potential in improving antidepressant drug delivery due to their characteristics [35]. The use of nanocarriers to improve the efficacy of delivery systems of antidepressants has gained increased attention among researchers [35].

1.2.5 Solid lipid Nanoparticles and Nanostructured lipid Particles

LNs are lipid-based and can overcome the limitations exhibited by the other colloidal carriers, due to good physical stability and excellent drug release profiles [36]. Moreover, LNs are biodegradable, easy to synthesize, non-toxic, and display controlled release properties. Due to their attractive characteristics, SLNs possess the potential to improve the efficacy of antidepressant drug delivery. SLNs display enhanced stability, improved bioavailability, improved epithelial permeability, prolonged half-life, enhanced permeability through the BBB, and reduced toxicity. Furthermore, LNs can be used to deliver both hydrophilic and lipophilic drugs, making them versatile drug delivery vehicles. They also have a large surface area due to their nano-sized feature, resulting in an improved absorption rate [37].

Solid lipid nanoparticles (SLNs) are considered to be an alternative carrier system to liposomes, emulsions, and polymeric micro-and nanoparticles. SLNs are spherical nanoparticles with a drug-containing solid lipid core stabilized with surfactants. SLNs enhance the bioavailability of drug molecules by some of the following potential mechanisms: (a) uptake of nanoparticles through the gastrointestinal (GI) tract directly; (b) enhanced permeability of intestinal membrane; (c) bioadhesion to the GI tract wall; and (d) stimulation of intestinal lymphatic transport. Apart from these, SLNs possess additional advantages viz., the possibility of encapsulating both lipophilic and hydrophilic drugs, biocompatibility because of biodegradable nature of lipids, controlled and/or sustained drug release rate, higher

drug content as compared to other carrier systems, improved stability of pharmaceuticals, water based technology, sterilizability, affordable feasibility in scale up, and suitability for oral, intravenous, pulmonary, ocular and transdermal administration.

The physicochemical properties of SLNs such as surface charge, size, lipophilicity, and surface property can be modified to enhance the penetration of SLNs across the gastrointestinal membrane. They also improve the oral bioavailability of drug molecules due to a decrease in the hepatic first-pass effect through the use of emulsifiers. Several studies have shown that SLNs could increase the oral bioavailability and therapeutic efficacy of antidepressants. Venlafaxine is a substrate of P-glycoprotein with lowered permeability through gastrointestinal and BBB. In one study, venlafaxine-loaded SLNs administered to mice via the oral route demonstrated a 1.5 fold higher concentration of the drug from SLNs in the brain and plasma when compared with venlafaxine alone. This data proved that SLNs can enhance the oral bioavailability of venlafaxine and its accumulation in the brain. The LNs also showed reduced P-glycoprotein-mediated efflux of venlafaxine, hence improving the penetration of the venlafaxine-loaded SLNs through the BBB. Moreover, an in vivo study using mice indicated that LN nanocarriers enhance the oral uptake of antidepressants by accessing the lymphatic system, hence improving oral bioavailability [38].

A potential drawback associated with SLN formulations is limited drug loading, drug leakage, and crystallization during storage. These problems were avoided or reduced by the development of a new generation of lipid nanoparticles, nanostructured lipid carriers (NLCs), wherein a solid lipid is blended with liquid lipid. An additional advantage of NLCs includes the possible modulation of drug release rate [39].

SLNs were modified by the incorporation of a liquid lipid into the solid structure to generate NLCs. The NLCs are considered a new generation of lipid nanoparticles. The technologies for NLC production are the same as that of SLN. The NLCs were introduced mainly to overcome the problems associated with SLNs, such as limited drug loading capacity and drug expulsion during storage. The NLC can be produced by the HPH method and the process can result in lipid particle dispersions having solid content ranging within 30 – 80%. NLCs formulated using ultrasound dispersion techniques have also been reported. The main components of NLC

formulations are lipids (solid and liquid), surfactants, and water. Various lipids and surfactants are used in NLC formulations.

The methods of NLC preparation are generally the same as those reported above for SLN formulations, the only difference being the introduction of liquid lipid in the NLC formulations. NLCs are also characterized by similar parameters as those reported for SLN formulations. NLC has been formulated for delivery through several routes including oral, topical, pulmonary, parenteral, transdermal, and ocular. Compared to other systems, NLCs favor higher drug loading, modulation of release, and improved drug inclusion. NLCs can be processed further into conventional dosage forms such as tablets, capsules, or pellets. NLC dispersions can also be filled into capsules and used for granulation or as a wetting agent in pellet production because of their greater particle concentration.[39]

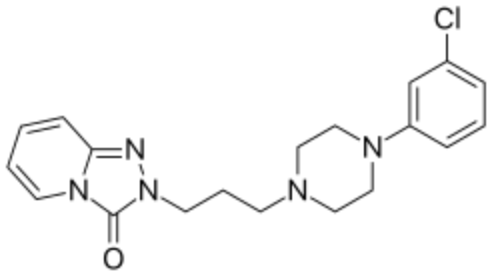
1.2.6 Surface Modification of Nanoparticles for Targeted Delivery of Antidepressants

Nanotechnology systems have gained considerable attention over the past years due to their attractive properties which include a high surface-area-to-volume ratio [40,41]. However, nanoparticles possess limitations such as instability when exposed to biological fluids and lack of specificity [40]. There is therefore a pressing need to modify the nanoparticle-based drug delivery systems to improve drug efficacy. Surface modification of nanoparticles has gained vast attention due to the important properties conferred on the particles which include improved drug specificity, nanoparticle circulation time, safety, biocompatibility, and solubility of hydrophobic drugs [42-44]. Most nanoparticles that are prepared from hydrophobic polymers are hydrophobic by default. Hence, it is important for them to be modified accordingly and targeted to the required sites. This can be done by coating the nanoparticles with biopolymers such as PEG and complexing them with ligands such as transferrin [45-46]. The coating of nanoparticles stabilizes them with no significant change in particle size). In addition, the coating of nanoparticles with hydrophilic polymers improves the circulation time, while the conjugation of nanoparticles with a ligand also improves the specificity of antidepressants [45-46], thereby improving the bioavailability and efficacy of the antidepressants.

1.2.7 Drug Profile

Trazodone Hydrochloride[47]

Trazodone Hydrochloride is the hydrochloride salt form of trazodone, a synthetic triazolopyridine derivative with antidepressant and sedative properties.



.Hcl

Figure 1: Chemical Structure of Trazodone Hcl

- Empirical formula: $C_{19}H_{22}ClN_5O$ HC1
- Molecular Weight: 408.33
- Melting Point: 222-228^{o}C
- Solubility: Trazodone hydrochloride is soluble in chloroform, sparingly soluble in water, ethanol and methanol and insoluble in common organic solvents.
- Dissociation constant: Trazodone is a weak base with a pKa of 6.14
- UV Spectrum: The spectra in methanol show maxima at 278 nm.
- BioavailabilityBy mouth: 50-65%
- Half life: Plasma concentrations of trazodone in man decline in a biphasic manner with a mean half-life of approximately 4 hours
- Mechanism of action: Trazodone is a mixed agonist and antagonist of various serotonin receptors, antagonist of adrenergic receptors, weak histamine H1 receptor antagonist, and weak serotonin reuptake inhibitor.
- Use: The primary use of trazodone is the treatment of major depression [47].

1.3 Factors Prompting to undertake the research project

There are various factors to undertake this research. The details of the factor are as follow:

1.3.1 Limited bioavailability of the conventional therapy

BBB is one of the main reasons why the delivery of therapeutic molecules inside the brain are so complex. The presence of the BBB is certainly the most critical issue encountered in brain drug delivery. The tight junctions of the endothelial cells make almost impossible each attempt of delivering drugs into the brain if they are not functionalized with specific targeting segments or if they are not encapsulated inside other nanostructures.

Brain capillaries, differently from the peripheral capillaries, present no fenestrae, a low amount of pinocytosis vesicles, and particular tight junctions (TJs) also known as zonula occludens. TJs are structures that form a narrow and continuous seal surrounding each endothelial and epithelial cell at the apical border and are aimed at strictly regulating the movement of molecules through the paracellular pathway. The BBB endothelial TJs show some differences in morphology, composition, and complexity features from those of both the epithelial and peripheral endothelial. These structures, together with the brain endothelial cells, make an almost impermeable barrier for drugs administered through the peripheral circulation. The P-glycoprotein (P-GP) is an ATP-dependent drug transport protein present at the apical membranes of different epithelial cell types including those forming the BBB. It was demonstrated, both in vitro and in vivo, that BBB P-GP can prevent the accumulation of many molecules including a variety of drug [48].

1.3.2 High accumulation of the drug in brain parenchyma through lipid nanoparticles (SLN and NLC)

The literature revealed that both solid lipid nanoparticles and nanostructured lipid particles increase the accumulation of drugs in the brain parenchyma. But Unfortunately, only a small amount of papers deeply investigated the mechanisms underlying LN brain targeting. Among the possible proposed mechanisms explaining drug accumulation in the brain parenchyma, the most likely accounts for preferential protein adsorption on particle surface due to the presence of specific surfactants, namely P80 and P188. In particular, the apolipoproteins A-I, B, and E adsorption have been correlated to a significant improvement of the pharmacologic effect of several drugs. This hypothesis is supported by the presence of specific receptors (e.g., scavenger receptor class B type I and low-density lipoprotein receptors) on the BBB luminal side, aimed at the endocytosis and transcytosis of low-density lipoproteins [48].

1.3.3 Dominance of current pendamic Covid 19

At present Ever since the pandemic hit India over five months back, followed by unprecedented lockdown, the stress level has been a rise on the 43 percent of Indian suffering from depression.

Advantage of lipid nanoparticles including SLN and NLC over another delivery system. Lipid nanoparticles combine the advantages of liposomes, concerning the low material toxicity, with that of polymeric NPs, in terms of controlled release. Lipids and waxes, due to their low toxicity and high biocompatibility, present potential advantages over synthetic polymers for the preparation of polymeric NPs.

1.3.4 Scaling up the feasibility of Lipid Nanoparticles (Solid lipid nanoparticles and Nanostructured lipid particles)

Solid lipid nanoparticles and Nanostructured lipid particles are a carrier system for cosmetic ingredients and pharmaceutical drugs which combines the advantages of either, liposomes or solid polymeric nanoparticles. No satisfactory and accepted scaling-up method exists for polymeric nanocapsules. Various methods are described, using e.g. supercritical fluids, but no large-scale method could be established to introduce polymeric nanoparticles to the pharmaceutical market. Liposomes and emulsions can be produced easily at a large scale by high-pressure homogenization. The same technique can be transferred to produce solid lipid nanoparticles or nanosuspensions. The disadvantages of emulsions and liposomes are their weak chemical and physical protection capacities of sensitive ingredients, such as vitamins. SLN consists of a matrix made from solid lipids which are stabilized in aqueous dispersion by surfactants or polymers, and the dispersion can be transferred to a dry product by spray-drying or lyophilization. Solid lipid nanoparticles can combine the physical integrity of particle shape as well as the chemical and physical stabilization of fragile ingredients. Furthermore, the ingredient or excipients that have been used in the preparation of solid lipid nanoparticles and nanostructured lipid particles are cheap in cost and easily available [49].

1.3.5 Lipid nanoparticle suitable candidate for the oral delivery of drug

The gastrointestinal (GI) tract acts as a physiological and chemical barrier setting several challenges for oral drug delivery systems (DDS). The organization of SLN is conceivable as an aqueous dispersion by changing it into a traditional dosage form, like tablets, pellets, capsules, or powder. Which are utilized to shield the drug from the harsh condition of the gastrointestinal tract and improve the permeability of the drug over the intestinal hindrance without increased toxicity expanded toxicity. SLNs have absorbed in the GI tract Accordingly, SLNs in a prolonged moment release the encapsulated drug with the help of the enterocyte membrane. Furthermore, due to lymphatic pathway avoid the first-pass metabolism of drug and release drug in the systemic circulation [50]

REVIEW OF LITERATURE

2. Review of Literature

He *et.al.*, (2021) developed Solid lipid nanoparticles loaded with curcumin and dronabinol to treat major depressive disorder. Dexanabinol (HU-211) is an artificially synthesized cannabinoid derivative that exerts neuroprotective effects through anti-inflammatory and antioxidant effects. Curcumin exhibits antidepressant effects in the treatment of the major depressive disorder. To investigate the antidepressant effects of solid lipid nanoparticles loaded with both curcumin and dronabinol, and the underlying mechanisms associated with this combination, we established wild-type (CBR1) and cannabinoid receptor 1 (CBR1) knockout (CBR1) mouse models of major depressive disorder, through the intraperitoneal injection of corticosterone, for 3 successive days, followed by treatment with intraperitoneal injections of solid lipid nanoparticles loading with curcumin (20 mg/kg) and dronabinol (0.85 mg/kg), for 2 successive days. Our results revealed that solid lipid nanoparticle loading with curcumin and dronabinol increased the mRNA and protein expression levels of the mature neuronal markers neuronal nuclei, mitogen-activated protein 2, and neuron-specific beta-tubulin III, promoted the release of dopamine and norepinephrine, and increased the mRNA expression of CBR1 and the downstream genes Rasgef1c and Egr1, and simultaneously improved rat locomotor function. However, solid lipid nanoparticles loaded with curcumin and dronabinol had no antidepressant effects on the CBR1 mouse models of major depressive disorder.[51]

Elhesaisy *et.al.*, (2020) developed and characterized the antidepressant effect of the trazodone hydrochloride-loaded lipid core polymeric nanoparticle. Trazodone hydrochloride (TRH) is a lipophilic drug that is used effectively as an antidepressant. Its poor solubility and short half-life represent an obstacle to its successful use. Nanocapsules with biodegradable polymeric shells are successful drug delivery systems for controlling the release of drugs. To enhance the entrapment of lipophilic drugs, oils can be added forming a lipophilic core in which the drug is more soluble. This study aimed to enhance the efficacy of TRH and prolong its action by formulating it into lipid core polymeric shell nanocapsules. Nanocapsules were prepared using the nanoprecipitation technique. All prepared formulations were in the nanosize range and negatively charged. The TRH entrapment efficiency (EE%) in lipid core nanocapsules was up

to 74.8 ± 0.5% when using Labrafac lipophile as a lipid core compared to only 55.7 ± 0.9% in lipid-free polymeric nanospheres. Controlled TRH release was achieved for all prepared formulations. Forced swim test results indicated the significant enhancement of the antidepressant effect of the selected TRH-loaded Labrafac lipophile core nanocapsules formulation compared to control and TRH dispersion in phosphate buffer. It is concluded that lipid core nanocapsules are a promising carrier for the enhancement of TRH efficacy [52].

Vitorino *et.al.*,(2020) described the preparation of lipid nanoparticles using the QbD approach for the treatment of depression. They developed this to design an antidepressant therapeutic surrogate relying on a dual strategy supported on lipid nanoparticles and intranasal delivery. For that purpose, the formulation was comprehensively optimized following a quality by design perspective. Critical quality attributes (CQAs) ranged from physicochemical to intranasal performance features. The optimized formulation was administered to mice to assess the anti-depressive and anxiolytic effects by applying the forced swimming and marble-burying tests, respectively. A cross-analysis of the predictive models established for the set of 12 CQAs elicited the formulation containing a similar proportion of solid and liquid lipids and lower surfactant concentration as the optimal one. Despite increasing the liquid lipid amount yielded smaller and more homogeneous particle size, and higher release rate, nanostructured lipid carriers (NLCs) provided an earlier and superior pig nasal mucosa permeability than nanoemulsions, along with better stability and cytotoxic profiles. Importantly, the intranasal delivery of the optimal lipid nanoparticle formulation reduced both depressive and anxiety-like behaviors, which positions these intranasal nanosystems in line with the hypothesis of provisioning timely and better-acting antidepressant therapies [53].

Kumar *et.al.*, (2019) prepared Methylthioadenosine loaded solid lipid nanoparticles for brain targeting through the oral route of administration. They demonstrated the application of solid lipid nanoparticles for the management of neurological conditions like multiple sclerosis. The stearic acid–based SLNs were below 100 nm with almost neutral zeta potential and offered higher drug entrapment and drug loading. Cuprizone-induced demyelination model in mice was employed to mimic multiple sclerosis-like conditions. It was observed that the MTA-

loaded SLNs were able to maintain the normal metabolism, locomotor activity, motor coordination, balancing, and grip strength of the rodents in substantially superior ways vis-à-vis plain MTA. Histopathological studies of the corpus callosum and its subsequent staining with myelin staining dye luxury fast blue proved the potential of MTA-loaded SLNs in the remyelination of neurons. The pharmacokinetic studies provided evidence for improved bioavailability and enhanced bioresidence supporting the pharmacodynamic findings. The studies proved that SLNencapsulated MTA can be substantially delivered to the brain and can effectively remyelinate the neurons. It can reverse multiple sclerosis-like symptoms in a safer and effective manner, that too by oral route [54].

Shirodkar *et.al.*, (2019) demonstrated the emerging of solid lipid nanoparticles and nanostructured lipid particles as drug delivery systems. In recent years, two lipid-based nanoparticles, namely solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are widely explored. SLN are spherical nanoparticles with a drug-containing solid lipid core stabilized with surfactants and formulated mainly to improve the bioavailability of the drug molecules. Despite several advantages of SLNs, their major drawbacks include limited drug loading, drug leakage, and crystallization during storage. These drawbacks were avoided or reduced by the development of a new generation of lipid nanoparticles, the NLC, wherein a solid lipid is blended with liquid lipid. Modulation of drug release was added advantage with NLC formulations. The present review focuses on production techniques, characterization, release characteristics, stability, toxicity, and potential applications of SLNs and NLCs [39].

Ghasemiyeh *et.al.*, (2018) explained the Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems. During the recent years, more attentions have been focused on lipid base drug delivery system to overcome some limitations of conventional formulations. Among these delivery systems solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are promising delivery systems due to the ease of manufacturing processes, scale up capability, biocompatibility, and also biodegradability of formulation constituents and many other advantages which could be related to specific route of administration or nature of the materials are to be loaded to these delivery systems. The aim

of this article is to review the advantages and limitations of these delivery systems based on the route of administration and to emphasis the effectiveness of such formulations [55].

Misiuk *et.al.*, (2009) investigated the formation and in vitro characterization of inclusion complex of trazodone hydrochloride with hydroxypropyl-b-cyclodextrin. They investigated the formation of the Inclusion complex of trazodone hydrochloride (TRD) with hydroxypropyl-b-cyclodextrin (HP-BCD) by 1H NMR, 13CNMR, 2D NMR, FTIR, and UV/visible spectroscopy. It was testified that the inclusion complex was formed between HP-BCD and trazodone. The stability constant K1:1 and the 1:1 stoichiometry of complexation were determined. NMR analysis confirmed the inclusion and provide information on the behavior of TRD inside the cavity of HP-BCD. It was found that the fragment of the TRD molecule, the benzene ring entered into the cavity of HP-BCD. Concerning the structure of the inclusion complex, the orientation of trazodone in the hydroxypropyl-b-cyclodextrin cavity has been confirmed by2D NMR spectroscopy. Based on the enhancement of the absorbance of trazodone produced through complex formation, a spectrophotometric method for the determination of trazodone in bulk aqueous solution in presence of HP-BCD was developed, which overcome the effect of condition change on the determination of trazodone. The linear relationship between the absorbance and trazodone concentration was obtained in the range of 5–30µg/ml with a correlation coefficient of 0.9998. The detection limit was 0.27 µg/ml [56].

Muchow *et.al.*, (2008) explained the application of Lipid Nanoparticles as a drug delivery system for the oral route of administration. Solid lipid nanoparticles (SLN®), nanostructured lipid carriers (NLC®), and lipid–drug conjugates (LDC®), commonly produced by high-pressure homogenization, are interesting vectors for oral delivery of lipophilic and, to a certain extent, hydrophilic substances. Their production can be done without the use of organic solvents. Techniques to make them a physically stable delivery system have been developed. Scaling up the production process from lab-size to large-scale dimensions using high-pressure homogenization can be easily achieved by using a different type of homogenizer. The machines used for largescale production often yield an even better product quality than the lab-scale types [57].

AIM AND OBJECTIVE

3.0 Novelty behind the Research & Aim and Objective

3.1 Novelty behind the Research

Depression is one of the most common, chronic, and debilitating psychological disorders that may lead eventually to patient suicide. It is characterized by many symptoms like feeling hopelessness or inappropriate guilt, low energy, change in sleep, change in appetite, and recurrent thoughts of suicide. Its consequences not only affect the patient but also affect negatively the whole society. The financial consequences of this disease are tremendous and cause an overwhelming burden on society. This burden is due to the dramatic decrease in productivity and absenteeism in the workplace. Depression mainly occurred due to the deficiency of both serotonin and norepinephrine neurotransmitters in the brain. Trazodone hydrochloride (TRH) is one of the most potent drugs used for the treatment of depression. It is a triazolopyridine derivative with an antidepressant effect. It is thought that the mechanism of action of TRH is due to its activity at 5-HT1, 5-HT2 serotonergic receptors. It also acts on poorly blocking serotonin reuptake and selectively blocking presynaptic receptors. In addition, TRH blocks alpha-2 adrenoceptors. TRH possesses unique properties compared to other antidepressants. TRH causes fewer anticholinergic side effects compared to the tricyclic antidepressant. It also has an activity against anxiety which is concomitant to depressed patients. Several studies showed that at therapeutic doses TRH is less likely to cause cardiotoxicity than imipramine. TRH also does not result in neurologic side effects and seems to be well tolerated by elderly. Despite all of these unique properties of TRH, it suffers from some drawbacks that negatively affects its activity. It is a small molecule of molar mass 408.33 g/mol and it has high lipophilic nature. TRH has a very short half-life about 4.1 h. This leads to frequent administration of TRH which decreases depression patients' compliance and their adherence to the treatment regimen. Also hydrophobic small molecule drugs suffer from low water solubility and wide tissue distribution profile which may lead to very serious side effects after administration of free drug. Nanotechnology has become one of the main technologies of the 21st century as a result. Formulation approaches including the use of Poly (ε-caprolactone) Nanocapsules, beta cyclodextrin complex utilized to overcome low aqueous solubility, dissolution, oral bioavailability and for brain delivery of trazodone hydrochloride.

However, none of the previously reported studies investigated the in vivo antidepressant effects of trazodone hcl-loaded solid lipid nanoparticles and Nano structure lipid particle after oral administration [52].

Nanoparticle-based drug delivery systems were considered as suitable delivery system to increase oral bioavailability. Lipid nanoparticles such as SLNs and NLCs have the advantage of sustained drug release capability to maintain a constant plasma levels. In addition, nanoparticles with higher specific surface area and higher saturation solubility have more rapid dissolution rate that can accelerate the onset of drugs action. Other major barriers in oral drug delivery are p-glycoprotein efflux pumps and chemical or enzymatic degradation. Recent researches have shown that some specific lipids or surfactants, which are used in lipid nanoparticles, are capable of inhibiting p-glycoprotein efflux pumps. Drug-loaded lipid nanoparticles could reduce chemical or enzymatic degradation of the drugs which are embedded in a lipid matrix. Lipid nanoparticles could promote lymphatic transport and can bypass the liver and avoid hepatic first pass effect [54].

SLNs are the first generation of lipid nanoparticles composed of solid lipid core covered by a surfactant shell to stabilize the system. SLNs are preferred over their colloidal counterparts due to a number of advantages including biocompatibility, high drug incorporation, sustained drug release, improved physical and chemical stabilities, enhanced drug protection in physiological environment, improved bioavailability and convenient large scale production. More importantly, owing to their small particle size and lipid nature, SLNs have the inherent ability to penetrate the BBB even without any surface functionalization. Considering their favourable attributes, SLNs could be a promising drug delivery system for improving the brain delivery of Trazodone Hcl [57].

Similarly Nanostructured lipid carriers (NLCs) represent another interesting type of lipid nanocarrier, planned with the purpose of improving some potential shortcomings presented by SLNs, especially their propensity to throw out the drug from the matrix during the storage, due to the highly ordered status of the crystalline solid lipid. In fact, differently from SLNs, the solid matrix of NLCs is formed by a mixture of biocompatible solid and liquid lipids, thus giving rise to a less-ordered, imperfect structure, which should ensure improved physical

stability, higher drug loading ability and lower tendency to prematurely leak the drug during storage [57].

There are several mechanisms through which the both NLC and SLN increase the bioavailability though oral route administration. Different mechanisms have been suggested for the oral bioavailability enhancing property of nanoparticulate drug carriers. One of these mechanisms is the general adhesiveness of nanoparticles to the gastrointestinal mucosa and release of the drug at the exact place of absorption. The second mechanism suggested is applicable for any lipid-based drug delivery system including emulsions, self-emulsifying formulations, and lipid nanoparticulate matrix systems. The lipids after oral administration are broken down by lipolytic enzymes pancreatic lipase and its cofactor co-lipase to diglyceride, monoglyceride, and fatty acid. The presence of lipids in small intestine stimulates the gall bladder to secrete bile salt, phospholipid, and cholesterol. The monoglyceride, fatty acid, and lysophospholipid produced by the lipolysis are thereafter solubilized with the help of the bile salts by incorporation into multilamellar and unilamellar vesicles, mixed micelles and micelles. The lipid digestion products and drugs dissolved in the lipids are solubilized in these micelle and mixed micelle leading to a significant increase in dissolution and absorption of the solubilized species. An unstirred water layer separates the brush border (apical) membrane of enterocytes from the bulk fluid phase of the small intestinal lumen. This layer is separate from the luminal bulk phase and forms an acidic microclimate adjoining the enterocytes together with the mucus layer. This unstirred layer poses a major barrier to the diffusion of lipids and lipophilic molecules owing to their negligible solubility in water. Micellar solubilization of fatty acid, monoglycerides, and lipophilic molecules greatly improves their solubility in the unstirred water layer and aids in their transport across the stagnant layer. Micelles cannot be absorbed as such across the epithelial membrane. The acidic pH of the unstirred water layer microclimate might facilitate micellar dissociation and solutes should first leave the mixed micellar phase before it can partition into the epithelial cells. The free fatty acid, monoglyceride, and lipid soluble molecules can partition across the brush border membrane by simple passive diffusion or by active transport or might be subjected to efflux transport by efflux transporter. The absorption enhancing effect of the lipid depends on the chain length of

the lipid used and generally LCTs exert a more profound effect than MCTs. Another possible mechanism by which lipidic excipients enhance oral bioavailability is lymphatic transport [56-58].

Considering these advantages of SLN and NLC, it seemed worthy of interest to further investigate and compare the effectiveness of SLNs and NLCs as carriers for the development of suitable or formulations of Trazodone hcl, by particularly focusing the attention on the proper choice of the most effective solid and liquid lipid components and carefully investigating the effect of different surfactants, also in combinations and at different amounts, in order to optimize the nanoparticle properties (in terms of size, homogeneity, entrapment efficiency and storage stability).

The literature revealed that both solid lipid nanoparticles and nanostructured lipid particles increase the accumulation of drugs in the brain parenchyma through receptor mediated absorption mechanism or the endocytosis and transcytosis mechanism.

3.2 Aim

The aim of the present study was to prepare Trazodone hydrochloride loaded solid lipid nanoparticle and Nano structured lipid particles capsules to improve the half-life and to produce sustained release of drug for the treatment of depression.

3.3 Objective

- To sustained the release of the drug
- To improve the half-life of the drug
- To improve the patient compliance
- To study the existence of the trazodone hydrochloride in lipid matrix
- To compare the result of solid lipid nanoparticle and Nanostructured lipid particles

HYPOTHESIS

4.0 Hypothesis

As estimated by W.H.O, depression shall become the second largest illness in terms of morbidity by another decade in the world, already one out of every five women, and twelve men have depression. Not just adults, but two percent of school children, and five percent of teenagers also suffer from depression, and these mostly go unidentified. Depression has been the commonest reason why people come to a psychiatrist, although the common man's perception is that all psychological problems are depression. Trazodone (TRZ) is effective in patients with major depressive disorders and is generally more useful in depressive disorders associated with insomnia and anxiety. It is thought that the antidepressant properties of TRZ may be related to its action on poorly blocking serotonin reuptake and selectively blocking presynaptic receptors as well as having activity at 5-HT1, 5-HT2 serotonergic receptors. In addition, TRZ blocks alpha-2 adrenoceptor. The oral bioavailability of trazodone conventional tablets is 50-60%. The bioavailability is limited by the presence of the blood-brain barrier and poor solubility in the physiological media. In order to improve the bioavailability of conventional tablets, the solid lipid nanoparticle and Nanostructured lipid particle could be good candidates got brain delivery because they could not only improve the oral bioavailability of the trazodone hcl but also increase the accumulation of drug into the brain cells as oral administration. On the basis of previous work related to the application of solid lipid nanoparticle nanostructured lipid, we can hypothesize that the trazodone Hcl loaded solid lipid nanoparticle and nanostructured lipid particle would enhance the oral bioavailability of trazodone Hcl.

RESEARCH METHODOLOGY

5.0 Research Methodologies

5.1 Preparation of SLN and NLC

The stearic acid SLN and NLC with or without drugs were prepared by solvent diffusion method in an aqueous system reported in our previous study. Briefly, 190 mg SA (0 wt% OA) or a mixture of OA and SA (OA–SA) with 5, 15, 30, and 45 wt% OA content, respectively, were prepared by adding OA to SA. Prepared 190 mg SA or OA–SA and drug were then completely dissolved into a mixture of acetone (6 ml) and ethanol (6 ml) in a water bath at 70 ◦C. The resultant organic solution was quickly dispersed into 120 ml distilled water under mechanical agitate with 400 rpm in a water bath at 70 ◦C for 5 min. The obtained pre-emulsion (melted lipid droplet) was then cooled at room temperature till drug-loaded SLN or NLC dispersion was obtained. The drug-free SLN or NLC dispersion was prepared exactly the same manner only replacing drugs by 10 mg SA or OA–SA [59].

The SLN or NLC was redispersed in distilled water (1.0% of lipid content, w/v), and the resultant dispersion was fast frozen under −75 ◦C in a deep-freezer for 5 h and then the sample was moved to the freeze-drier. The drying time was controlled in 72 h and then the SLN or NLC powders were collected for DSC and in vitro release experiments.

5.2 In vitro characterization of SLN and NLC [59]

5.2.1 Particle size and zeta potential measurement

The volume average diameter and zeta potential of drug-free or drug-loaded nanoparticles in dispersion were determined with Zetasizer after diluted 20 times with distilled water.

5.2.2 TEM examination

The morphological observation of drug-loaded nanoparticles was performed by transmission electron microscopy (TEM). The samples were diluted for TEM observation.

5.2.3 DSC analysis

Differential scanning calorimetry (DSC) analysis was performed using DSC. For DSC measurement, 10 mg of powdered drug-free nanoparticles were put in aluminium pans. A scan rate of 10 ◦C/min was employed in the 20–80 ◦C temperature range.

5.2.4 Drug entrapment efficiency determination

The drug loaded nanoparticles were dispersed in an 80 ml solution and surged vortically for 3 min to dissolve the free drugs. The resulting dispersions were centrifuged for 20 min at 25,000 rpm. The drug content in the supernatant after centrifugation was measured by uv method

5.2.5 In vitro release assay

The drug release profiles from nanoparticles were measured in vitro. Fifteen milligrams of powdered SLN or NLC were dispersed in 30 ml Dissolution media in 50 ml appropriate glass test-tube. The resulting samples were surged vortically for 3 min, and then shaken horizontally at 37 ◦C and 60 strokes per min. One millilitre of the dispersion was withdrawn from the system at definite time interval and filtrated with 100 nm filter. The filtrate was determined by the UV method as described above.

PLAN OF WORK

6.0 Plan of work

6.1 Review of Literature

6.2 Preformulation studies of drug

- Organoleptic characterization
- Melting Point
- Determination of λ max and Standard curve
- UV method development and Validation
- Solubility of drug
- Lipid solubility of drug
- Partition coefficient of drug
- FTIR Spectra
- Drug-excipients compatibility study
- DSC and XRD (Drug, excipients and Physical mixture)

6.3 Preparation of Drug loaded solid lipid nanoparticle and Nanostructured lipid particles formulations

6.4 Optimization of Drug loaded solid lipid nanoparticle and Nanostructured lipid particles formulations using the QbD approach

6.5 In vitro Evaluation of drug loaded solid lipid nanoparticle and Nanostructured lipid particles

- Percentage Yield
- Particle Size and Zeta Potential
- Drug entrapment and Percentage drug loading

6.6 Development of the Drug loaded SLN and NLC containing capsule

6.7 In vitro Evaluation of drug loaded solid lipid nanoparticle and Nanostructured lipid particles containing capsule

- FTIR, DSC, XRD of optimized formulation
- Percentage Yield
- Particle Size and Zeta Potential
- Drug entrapment and Percentage drug loading

- TEM of optimized formulation
- In-Vitro drug release study
- In vitro drug release kinetic study

6.8 Stability study of the drug loaded solid lipid nanoparticle and Nanostructured lipid particles containing capsule

6.9 In vivo antidepressant activity of drug loaded solid lipid nanoparticle and Nanostructured lipid particles containing capsule

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Abhilashi University, Chail - Chowk (Mandi)

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Name of School: School of Pharmacy
Subject: Pharmaceutics

1. Name (IN BLOCK LETTERS): Mrs. NEHA SHARMA

   (a) Father's Name: Shri Surinder Pal Sharma

   (b) Mother's Name: Smt Anita Sharma

   (c) Registration Number: AU20PYPhD0040

2. School of the University/Approved Centre where research work will be carried out by the candidate……
   ……

3. Date of Registration:

4. Tentative title of thesis/ broad area of research work "Orally Administered Trazodone Hydrochloride Loaded Solid Lipid Nanoparticle and Nano Structured Lipid Particles for the Treatment Depression".

I am appending herewith ….. copies of the synopsis of my proposed research project, through the Dean/Coordinator/HOD of the Faculty/School. I further certify that I have thoroughly checked the spellings of the tentative title of the proposed thesis and found the same to be correct.

Date: …… ……..
(Full Signature of the Applicant)

Signature of the Supervisor Signature of the Dean/Coordinator/HOD

Recommendations of the Supervisor.

i) I give my consent to act as supervisor to Mr./Ms……in his/her research work for the Degree of Doctor of Philosophy (Ph.D.) in the School of ……

ii) I further recommend that :

   a) The proposed title/broad area of work/synopsis as mentioned above may kindly be approved.

iii) It is certified that the supervisor is covered under the relevant rules relating to number of candidates which could be guided by a supervisor/s (as contained Ph.D. guidelines of the University).

iv) It is further certified that the appointment of supervisor/s and tentative title of Ph.D. thesis/broad area of work have been duly recommended by the Departmental Research Committee of the Department/Approved Research Centre in their joint meeting held on …….

v) To register the candidate all the rules and regulations are followed as per Abhilashi University Ph.D. guidelines (as amended).

Signature/s, designation and address of supervisor/s

Recommendation of Dean/Coordinator/HOD

……..…….

..…….

……..…….

……..…….

Dated: ……

Signature (along with Seal of the Office)
of the Dean/Coordinator/HOD of the Faculty/School/Administrative Head of the

approved Research Centre